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Cardiovascular control in women with fibromyalgia syndrome: do causal methods provide non redundant information compared to more traditional approaches?

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Running Head: Causality and BRS in women with FMS

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ABSTRACT

The cardiovascular autonomic control and the baroreflex sensitivity (BRS) have been widely studied in fibromyalgia syndrome (FMS) patients through the computation of linear indices of spontaneous heart period (HP) and systolic arterial pressure (SAP) variabilities. However, there are many methodological difficulties regarding the quantification of BRS by the traditional indices especially in relation to the issue of causality. This difficulty has been directly tackled via a model-based approach describing the closed-loop HP-SAP interactions and the exogenous influences of respiration. Therefore, we aimed to assess if the BRS assessed by the model-based causal closed-loop approach during supine and active standing in patients with FMS could provide complementary information to those obtained by traditional indices based on time and frequency domains. The findings of this study revealed that, at difference with the traditional methods to quantify BRS, the causality analysis applied to the HP, SAP and respiratory series, through the model-based closed-loop approach, detected lower BRS in supine position as well as a blunted response to the orthostatic stimulus in patients with FMS compared to healthy control subjects. Also, the strength of the causal relation from SAP to HP (i.e., along the cardiac baroreflex) increased during the active standing only in the control subjects. The model-based closed-loop approach proved to provide important complementary information about the cardiovascular autonomic control in patients with FMS.

Keywords: Fibromyalgia; baroreflex; autonomic nervous system; modeling; causality

INTRODUCTION

Fibromyalgia syndrome (FMS) is a non-inflammatory syndrome characterized by chronic diffuse musculoskeletal pain, stiffness and pain hypersensitivity in 18 specific points located in muscles or tendon muscle insertion called tender points (27). Although the painful condition is the main characteristic of this syndrome, advancements regarding the etiology and pathophysiology of FMS has attributed an important role to dysautonomia (i.e. the autonomic nervous system dysfunction) (4, 7, 11, 12, 24, 25).

The dysautonomia has been widely demonstrated in patients with FMS. Thus, it is known that FMS patients present an alteration of the cardiac autonomic modulation characterized by a high cardiac sympathetic modulation and low cardiac parasympathetic modulation even at rest (4, 7, 11, 12, 24, 25). In addition, despite a normal baroreflex function, a lack of increased sympathetic discharge to vessels and decreased cardiac vagal activity has been reported during the orthostatic stimulus, which may account for the reduced orthostatic tolerance, commonly observed in these patients (7).

Traditionally, the baroreflex sensitivity (BRS) in FMS patients has been studied through the computation of indices derived from spontaneous heart period (HP) and systolic arterial pressure (SAP) variabilities (4, 7, 11, 12, 24, 25). However, these approaches to the quantification of BRS have many methodological drawbacks. The most relevant one is the inability of accounting for causality, thus merging the feedforward pathway from HP to SAP, more related to the mechanical properties of the heart and dynamical properties of circulatory system, to the feedback one, more related to cardiac baroreflex (18, 23)..

In attempt to overcome this issue, model-based causal closed-loop methods (1, 9, 13, 28), and more recently, a Granger causality approach have been proposed (18, 20, 22). These methods have shown to provide complementary information to that obtained by traditional indices about the cardiovascular autonomic regulation. This capability has been attributed to their ability to account for both feedforward and feedback pathways, for the effects of respiration and the issue of causality. Disregarding these factors usually hampers more traditional approaches to the description of the HP-SAP interactions.

Whether patients with FMS present a dysfunction in the baroreflex function is not clear. Reyes del Paso et al. (24) reported an overall reduction in the spontaneous cardiac baroreflex function in patients with FMS assessed by the sequence analysis based on continuous blood pressure and HP series recordings. On the other hand, Furlan et al (7) did not find any significant differences between patients with FMS and healthy control subjects, thus making controversial the issue of the quantification of BRS in FMS.

Thus, the aim of this study was to assess if the BRS assessed by the model-based causal closed-loop approach based on spontaneous HP and SAP variabilities during supine and active standing in patients with FMS could provide complementary information to those obtained by traditional indices based on time and frequency domains and shed light on the baroreflex control in FMS.

MATERIALS AND METHODS

Participants

Twenty six women with a clinical diagnosis of FMS and 20 healthy women took part in the study. The diagnosis was made by a board certified rheumatologist according to criteria established by the American College of Rheumatology (27). The subjects

with FMS were recruited from local community after they responded to flyers posted in university buildings, orthopedic and rheumatologic clinics, or from our database of FMS patients that enrolled to other studies. The control group (CG) was recruited from local community and through personal contacts of the investigators. Age and clinical characteristics of both groups are presented in Table 1.

>>> INSERT TABLE 1 <<<

To fulfill the inclusion criteria, subjects were not allowed to have a history of cardiovascular, respiratory or metabolic disease of any kind, inflammation as a cause of pain, neurological disorders, cognitive deficits that would prevent understanding and conducting the evaluations, they could not to be smokers or engaged in regular physical activity or make continuous use of drugs or alcohol. The study was approved by the Ethics in Research Committee and all participants gave written informed consent.

Experimental procedure

All experiments were carried out in the afternoon in order to minimize circadian changes. Room temperature was maintained at 22°C and relative air humidity at between 40% and 60%. Participants were acquainted with the experimental protocol and were instructed to abstain from stimulants (coffee, tea, soft drinks) and alcoholic beverages the 24 h preceding the examination, and to have a light meal at least two hours before the test. To avoid any residual fatigue, subjects were asked to refrain from strenuous physical activity at least two days before the tests. Participants had not taken any psychotropic or other medications known to alter autonomic activity for at least 4 weeks before the study, including antihypertensive drugs, tranquilizers, or antidepressants. The participants with regular menstrual cycle (28 ± 2 days) were assessed during the follicular phase, i.e., 7–10 days after the start of menses.

In every subject, we recorded the ECG (modified lead I) (BioAmp FE132, ADInstruments, Australia), noninvasive blood pressure (Finometer Pro, Finapres Medical Systems Ohmeda, Amsterdam, Netherland), and respiratory activity by a piezoelectric respiratory belt (Thoracic Belt, Marazza, Monza, Italy). The arterial pressure signal was cross-calibrated in each session by regularly measuring the blood pressure with a sphygmomanometer. Signals were digitalized using a commercial device (BioAmp Power Lab, AD Instruments, Australia) and sampled at 1000 Hz.

Data acquisition was performed during 15 minutes in supine resting position and during 15 minutes in orthostatic position reached by active standing. Before the beginning of data acquisition we allowed about 20 minutes for stabilization.

Extraction of the beat-to-beat variability series

The R-wave peaks were detected over the recorded ECG using parabolic interpolation. The temporal distance between two consecutive R-wave peaks was estimated as HP. The maximum of arterial pressure inside an HP was defined as SAP, and the i-th SAP [i.e., SAP(i)] was taken inside the i-th HP [i.e., HP(i)], where i is the cardiac beat counter. Respiratory (RESP) series was obtained by sampling the respiratory signal in correspondence with the R-wave peak. The i-th RESP [RESP(i)] was taken at the first R-wave peak delimiting HP(i).

The occurrences of QRS and SAP peaks were carefully checked to avoid erroneous detections or missed beats. HP = {HP(i), i = 1,... , N}, SAP = {SAP(i), i = 1,..., N} and RESP = {RESP(i), i = 1,..., N} were extracted on a beat-to-beat basis, where N is the series length. Sequences with N = 256 consecutive measures were selected inside supine and standing periods. According to the test proposed in Magagnin et al. (10) synchronous stationary sequences of HP, SAP and RESP values could always found.

Frequency domain BRS assessment

The power spectrum was estimated according to an univariate parametric approach fitting the series with an autoregressive (AR) model (17). AR spectral density was factorized into components, each of them characterized by a central frequency. If the central frequency of the component belonged to the low frequency band (LF, from 0.04 to 0.15 Hz) it was labeled as LF. The LF power was defined as the sum of the powers of all LF components.

The BRS estimated via spectral analysis was computed as the square root of the ratio of the LF power of HP on the LF power of SAP (17) and indicated as α_{LF} in the following. As prerequisites for the reliable estimation of BRS, two parameters were considered (17): 1) the HP-SAP correlation must be significant in the LF band i.e., the squared coherence function $K^2_{HP\text{-}SAP}(LF)$ should be higher than 0.5; 2) HP changes must lag behind SAP variations in the LF band, i.e., the phase of the cross-spectrum $Ph_{HP\text{-}SAP}(LF)$ should be lower than 0 with the adopted convention for the calculation of the HP-SAP cross-spectrum. The calculation of the BRS in the high frequency band (from 0.15 to 0.5 Hz) was not performed because the prerequisites for its calculation are fulfilled in a small percentage of subjects.

Time domain BRS assessment

Time domain assessment of the BRS was based on the detection of spontaneous sequences of 3 or more SAP and HP values that simultaneously increase (positive sequences) or decrease (negative sequences) (2). The lag between HP and SAP values was set to 0 in order to pick up the fast vagal arm of the baroreflex. Sequences were considered to reflect baroreceptor activity if the following criteria had been matched: 1) HP variations were > 5 ms; 2) SAP changes were > 1 mmHg; 3) sequences were longer than 4 beats. For each sequence, a linear regression of HP on SAP was computed, and

171 the slope of the regression line was calculated. In each subject, all the slopes with a
172 correlation coefficient > 0.85 were averaged and the final value taken as the gain of
173 arterial baroreflex control of heart rate and indicated as α_{SEQ} in the following.

174 *Closed-loop model-based estimate of the BRS and feedforward mechanical pathway*
175 *gain*

176 The BRS and the gain of the feedforward mechanical pathway were estimated
177 by the methodology reported in (1, 9, 18). Briefly, after identification of the coefficients
178 of the *M*-variate autoregressive model with $M = 3$ in Ω={HP, SAP, RESP}, the
179 baroreflex feedback arm, from SAP to HP, was described by the regression of HP on
180 past SAP values, whereas the regression of SAP on past HP values described the
181 mechanical feedforward arm, from HP to SAP. The two regressions accounted for the
182 possible common influences of RESP and memory effects of HP and SAP on their own
183 past values as well.

184 The goodness of fit of the model in fitting HP and SAP in Ω={HP, SAP, RESP},
185 indicated as ρ^2_{HP} and ρ^2_{SAP} in the following, was calculated after normalizing the series
186 to have unit variance as the complement to 1 of the mean square prediction error. The
187 model-based closed-loop estimate of the BRS was obtained by observing the response
188 of the relation from SAP to HP induced by an artificial increase of SAP with unit slope
189 (1, 9, 18). The corresponding slope of the HP increase was taken as an estimate of the
190 BRS and indicated as α_{CL} (1, 9, 18). Values larger than 0 were obtained when the HP
191 variation had the same sign of the SAP variation, as expected from a working
192 baroreflex. On the other hand, values lower than 0 might occur only in case of
193 activation of non-baroreflex mechanisms. The value of the first coefficient of the
194 regression from HP to SAP was taken as an index quantifying the gain of the
195 feedforward mechanical pathway from HP to SAP and was indicated as K_{CL}.

Granger-causality indices

A Granger causality approach (18, 20, 22) was utilized to assess, through the calculation of the causality ratio (CR), the strength of the causal relation from SAP to HP ($CR_{SAP\rightarrow HP}$) and from HP to SAP ($CR_{HP\rightarrow SAP}$) variability series in Ω. In this context, SAP is said to Granger-cause HP if the HP dynamics can be better predicted in Ω than in Ω={HP, SAP, RESP} after exclusion of SAP (i.e., Ω\SAP={HP,RESP}) (8). By simply reversing the role between HP and SAP it is possible to define the causality from HP to SAP. The inclusion of RESP in the minimal set of series is necessary to evaluate the HP-SAP causal relations, because RESP affects both HP and SAP (1, 19). Granger approach to the evaluation of causality from SAP to HP was described in detail elsewhere (18, 20). Briefly, defined the prediction error as the difference between the current HP value and its prediction based on the model, $CR_{SAP\rightarrow HP}$ is defined as the fractional decrement of the mean square prediction error of HP over the entire series due to the introduction of SAP in Ω\SAP. Thus, the more negative the $CR_{SAP\rightarrow HP}$, the higher the strength of the causal link from SAP to HP. The significance of $CR_{SAP\rightarrow HP}$ was checked by comparing the mean square prediction error of HP in Ω and in Ω\SAP via the F-test carried out over the absolute values of CR (26). If the $CR_{SAP\rightarrow HP}$ adjusted for the degrees of freedom (19, 26) was larger than the critical value of the F distribution for a significance level of 0.01, the null hypothesis that SAP did not Granger-cause HP was rejected and the alternative hypothesis of unidirectional causality from SAP to HP, indicated as SAP→HP in the following, was accepted (i.e., cardiac baroreflex is working). Reversing the role of SAP and HP allowed the calculation of $CR_{HP\rightarrow SAP}$ and the test of the null hypothesis that HP did not Granger-cause SAP. If the null hypothesis was rejected, the unidirectional causality from HP to SAP, indicated as HP→SAP in the following, was accepted.

Statistical analysis

Normal data distribution was verified by Shapiro-Wilk test. The Student independent t test was used to perform between group comparisons for age and clinical data. A two-way mixed design analysis of variance (ANOVA) was used to test for differences between groups in the hemodynamic, respiratory and baroreflex and closed-loop variables over the two postures (Group × Posture). When a significant Group × Posture interaction was observed, the interpretation of the main effects was not considered and pairwise comparisons were performed with Bonferroni adjustment. Effect size was reported using partial η2 (η_ρ^2). The nonparametric Pearson χ^2-test with Yates' correction for 2 × 2 contingency tables was used to assess the statistical significance of differences between groups regarding the percentages of subjects showing a given HP-SAP causal relation. Moreover, the McNemar χ^2-test was applied to verify the difference between supine and standing postures on the percentage of subjects exhibiting a given HP-SAP causal relation. Statistical significance was set at 5% for all tests. SPSS 20.0 (SPSS, Inc, Chicago, IL) was used for all analysis.

RESULTS

No significant differences were observed between CG and FMS group regarding age, body mass index and number of postmenopausal subjects. FMS group presented higher values for BDI, BAI, VAS scores and number of tender points (Table 1).

Table 2 summarizes the hemodynamic and respiratory variables of both groups. There was neither significant interaction between posture and group, nor significant main effect of group for any of these variables ($p>0.05$). A main effect of posture was found for heart rate ($F = 74.3$, $p = 0.0001$, $\eta_\rho^2 = 0.63$) and HP ($F = 85.6$, $p = 0.0001$, $\eta_\rho^2 = 0.66$).

Table 3 summarizes the baroreflex indices for both groups studied. Only a significant main effect of posture was found on α_{SEQ} ($F = 74.3$, $p = 0.0001$, $\eta_\rho^2 = 0.63$) and α_{LF} ($F = 74.3$, $p = 0.0001$, $\eta_\rho^2 = 0.63$). A significant posture x group interaction was found for α_{CL} ($F = 19.5$, $p = 0.0001$, $\eta_\rho^2=0.37$). Pairwise comparisons revealed that in supine posture, the CG presented higher values of α_{CL} compared to the FMS group ($p<0.05$). Regarding the comparisons between supine and standing postures, the CG presented a significant decrease of α_{CL} ($p<0.05$), which was not observed in the FMS group.

The goodness of fit of the models fitting HP and SAP is reported in Table 4. There was neither a significant interaction between posture and group, nor a significant main effect of group for ρ^2_{HP} and ρ^2_{SAP} ($p>0.05$). However, a main effect of posture was found for ρ^2_{HP} ($F = 5.84$, $p = 0.02$, $\eta_\rho^2 = 0.12$). The results indicate the ability of the models in describing the HP and SAP dynamics in any group and in any condition. The increase in the ρ^2_{HP} during the standing posture might be due to the increase of the regularity of the HP series.

Figure 1 displays the results relevant to the strength of causal relation from SAP to HP and vice versa. A significant posture x group interaction was found for $CR_{SAP\rightarrow HP}$ ($F = 4.97$, $p=0.03$, $\eta_\rho^2=0.11$). During active standing, the CG presented lower values of $CR_{SAP\rightarrow HP}$ compared to the FMS group ($p<0.05$) indicating that CG is characterized by a stronger strength of the relation from SAP to HP. In the comparisons between supine and standing postures, the CG presented a significant decrease of $CR_{SAP\rightarrow HP}$ ($p<0.05$) indicating an augmented strength of the relation from SAP to HP, which was not observed in the FMS group.

When K_{CL} and $CR_{HP \rightarrow SAP}$ were considered, there was neither a significant interaction between group and posture nor significant main effects of group and posture (Table 3 and Fig.1).

Figure 2 depicts the results of causality analysis displaying the percentage of subjects presenting a significant causal relationship from SAP to HP along the cardiac baroreflex pathway in supine and standing positions in the both groups. In supine position, 50% of the CG and 59% of the FMS group presented causal link from SAP to HP series along the cardiac baroreflex. During standing posture, the percentage of subjects presenting a causal link from SAP to HP series significantly increased in the CG (75%) and was higher compared to the FMS group (50%).

DISCUSSION

The main finding of this study is that, although the traditional methods to quantify the spontaneous baroreflex based on time and frequency domains approach did not show any significant differences between groups, the model-based closed-loop causality analysis applied to the HP, SAP and RESP series detected in supine position lower BRS and weaker strength of the baroreflex control. The blunted response to the orthostatic stimulus in patients with FMS compared to the CG was suggested by the decrease of BRS and the augmented strength of the causal relation from SAP to HP along the cardiac baroreflex observable only in the CG.

Considering the results of the BRS obtained by the traditional methods, our findings are in accordance with Furlan et al. (7), who reported no significant differences between patients with FMS and healthy controls, and disagree with those reported by Reyes del Paso et al (25), who reported an overall reduced BRS in FMS patients. A possible reason explaining this divergence may rely on the difference between the prerequisites required for BRS calculation regarding the sequence method. In the

present study we used the parameter setup for sequence analysis proposed by Bertinieri et al (2), which was the same setup used by Furlan et al. (7). This method requires as prerequisites in order to consider the sequences to reflect baroreceptor response HP variation >5 ms, SAP changes >1 mmHg, sequences longer than 4 beats and correlation coefficient >0.85. Conversely, in the method used by Reyes del Paso et al (24), they considered 2 ms as minimal criteria for changes in HP and no minimal value for correlation coefficient was required, since they stated that the mean slope of all detected SBP ramps was included in the analysis.

Regarding the results provided by the methods addressing causality and accounting for respiration, the findings are different from those obtained by the traditional methods. The strength of the causal relation from SAP to HP series increased in the CG during the active standing, indicating an increase involvement of the baroreflex in governing HP-SAP variability interactions during the orthostatic stimulus, which was not observed in the FMS group. Previous studies have shown that gravitational stimulus increases the involvement of baroreflex path on the control of heart rate (14, 21). A possible explanation relies on the unloading of cardiopulmonary baroreceptors consequent to the decrease of the central blood volume, leading to an activation of the cardiac baroreflex. Another possible factor that might play a role is the reduction of the venous return making the effect of respiration on arterial pressure more pronounced and resulting in a stronger activation of the cardiac baroreflex in the absence of significant changes of the mean SAP. Anyway, the results showed that a higher percentage of subjects with FMS did not elicited the baroreflex during active standing. Remarkable, this finding is already observable in resting condition. Moreover, the spontaneous baroreflex gain estimated by the closed-loop approach revealed higher values in CG subjects compared to FMS patients in supine posture. During the active

318 standing, the CG presented a reduction in the BRS gain, which was not observed in
319 FMS patients, since their baroreflex gain was already low in supine posture.

320 The reason to use the α_{CL} and the $CR_{SAP \rightarrow HP}$ indices in the present study is due to
321 the fact that they measure different aspects of a relation between variables (18, 22).
322 Whereas the $CR_{SAP \rightarrow HP}$ estimates the strength of the causal link from SAP to HP, thus
323 quantifying the degree of involvement of the baroreflex (22), α_{CL} estimates the gain of
324 relation from SAP to HP, i.e., the magnitude of the HP variation in response to a unit
325 SAP change. As a general rule BRS indexes should be considered reliably assessed only
326 when the baroreflex is active, i.e. when the strength of the relation from SAP to HP is
327 significant. An active baroreflex, characterized by a significant $CR_{SAP \rightarrow HP}$, might be
328 working, in principle, with either high or low BRS. Therefore, the two indexes convey
329 complementary information.

330 Thus, the FMS patients in the present study showed not only a diminished
331 baroreflex gain, but also a reduced intensity of the causal relation from SAP to HP
332 during standing, suggesting a reduction of the efficiency of the cardiac baroreflex
333 control.

334 Another important aspect of the model-based method (1, 9, 13, 28) is the
335 possibility to identify non-baroreflex mechanisms quantifying the gain of the
336 feedforward mechanical pathway from HP to SAP series. Based on modeling
337 approaches a prevalence of non-baroreflex interactions during supine position was
338 demonstrated (14, 21, 23). The present study confirms this observation. Indeed,
339 regardless the posture (supine or standing) or groups studied, the feedforward path is
340 active in most subjects. These findings may explain the divergence in the results
341 obtained by the α_{SEQ} and α_{LF} analyses, since they may have overestimated the
342 involvement of the baroreflex mechanism in governing HP-SAP interactions, especially

during supine posture, thus stressing the importance of accounting for causality in studies aiming to quantify the spontaneous baroreflex gain. As to the between-group comparison, indexes related to the mechanical feedforward did not show significant differences.

This study shed further light on the issue of autonomic nervous system in FMS. The sympathetic hyperactivity in FMS, well established in the literature (4, 7, 12), was attributed to a primary increase of central sympathetic drive, since it was unlikely to be due to a failure of the inhibitory modulation exerted by arterial baroreceptors. However, based on the present results, a deficient afferent baroreceptor feedback restraining the sympathetic activity may take place in these patients. On the other hand, it must be taken in account that the relationship between baroreceptor activity and sympathetic activity is bidirectional: an increase of sympathetic activity might be an effect of a baroreflex unloading as well as a direct effect of a central sympathetic drive restraining, as a consequence, baroreflex activity (16), thus supporting that the reduced baroreceptor function observed in the fibromyalgia patients might result from a central primary sympathetic hyperactivity previously hypothesized (7).

Even though, it was not possible to clarify if the reduced BRS leads to the sympathetic hyperactivity in FMS, this study has an important clinical implication regarding the risk of hypertension in this population. Some studies have found that chronic pain might be associated with increased prevalence of hypertension (3, 15). Moreover, Ducher et al. (6) found that a lower BRS was a consistent predictor for increase in SAP at 5 years of follow-up. In addition, Dauphinot et al. (5) found that increased BRS reduces the risk of day-time hypertension, and suggest that BRS may represent an intermediate goal to be considered by clinicians aiming the prevention of

hypertension. Thus, the findings of the present study drew the attention to the risk of hypertension in subjects with FMS, which should be addressed in futures investigations.

In conclusion, Granger causality linear model-based approach assessing the spontaneous HP and SAP variabilities interactions provides non redundant information compared to more traditional indices, based on time and frequency domain approaches, by revealing a reduced BRS in FMS patients, a reduced strength of the baroreflex control as well as a blunted response to the orthostatic stimulus.

PERSPECTIVE AND SIGNIFICANCE

Advanced signal processing techniques were found helpful in typifying the impaired cardiac baroreflex control in subjects affected by fibromyalgia syndrome and in detecting their reduced response to an orthostatic stimulus above and beyond more traditional indexes. These findings point to the possible role of a depressed baroreflex control in deteriorating the condition of these patients and suggest that the exploitation of countermeasures or therapies improving baroreflex control might have beneficial effects.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: A.R.Z. and E.S. conception and design of research; A.R.Z., C.P.A., M.F., A.M.C. and E.S. performed experiments; A.R.Z., A.M., and C.P.A. analyzed data; A.R.Z., A.P., A.M., F.B., R.F., A.M.C. and E.S. interpreted results of experiments; A.R.Z., A.P. and F.B. prepared figures; A.R.Z., A.M. and A.P. drafted manuscript; A.R.Z., A.P., C.P.A., A.M., M.F., F.B., R.F., A.M.C. and E.S., approved final version of manuscript.

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496 **Figure Legends**

497

498 Fig. 1. Bar graph of the causal ratio (CR) from systolic arterial pressure (SAP) to heart
499 period (HP) series and from HP to SAP in the control group (CG) and fibromyalgia
500 syndrome group (FMS) during supine and standing phases. Error bars indicate the
501 standard deviation. * $P < 0.05$ vs. SUPINE CG; # $P < 0.05$ vs STANDING FMS.

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505 Fig. 2. Bar graph of the percentage of subjects of the control group (CG) and
506 fibromyalgia syndrome group (FMS) presenting a significant causal interaction from
507 systolic arterial pressure (SAP) to heart period (HP) (i.e. SAP→HP) during supine and
508 standing phases.* $P < 0.05$ vs. SUPINE CG; # $P < 0.05$ vs STANDING FMS.

509

510 Table 1. Age and clinical characteristics of the control (CG) and the fibromyalgia syndrome
511 (FMS) groups.

	CG (n = 20)	FMS (n = 26)	p-value
Age (years)	46 ± 7	48 ± 7	0.33
BMI (Kg/m^2)	24.7 ± 3.0	26.1 ± 2.5	0.18
Number of postmenopausal women (n)	4	6	0.91
Disease duration (years)	-	8.0 ±5.1	-
FIQ score	-	62.7 ± 15.5	-
BDI score	6.2 ± 5.5	18.2 ± 7.4	<0.0001
BAI score	4.5 ± 3.9	20.6 ± 11.9	<0.0001
VAS Pain (mm)	1.4 ± 1.3	46.9 ± 24.0	<0.0001
Tender points	8.7 ± 3.2	17.2 ± 1.4	<0.0001
Pain pressure threshold (kg/cm^2)	3.6 ± 0.9	1.9 ± 0.5	<0.0001

512 BMI: body mass index; FIQ: Fibromyalgia Impact Questionnaire; BDI: Beck
513 Depression Inventory; BAI: Beck Anxiety Inventory; VAS: visual analogue scale.

514 Table 2. Hemodynamic and respiratory measures of the control (CG) and the fibromyalgia syndrome (FMS) groups.

	Supine		Standing		P	G	I
	CG	FMS	CG	FMS			
HR (bpm)	66 ± 8	67 ± 7	76 ± 8	73 ± 9	< 0.05	ns	ns
HP (ms)	913 ± 111	912 ± 98	806 ± 113	828 ± 100	< 0.05	ns	ns
SAP (mmHg)	117 ± 12	122 ± 25	125 ± 17	122 ± 25	ns	ns	ns
DAP (mmHg)	66 ± 7	66 ± 8	74 ± 9	70 ± 8	ns	ns	ns
Respiration (cycles/min)	17 ± 2	17 ± 2	17 ± 2	16 ± 2	ns	ns	ns

515 P: posture main effect; G: group main effect; I: interaction; HR: heart rate; HP: heart period; SAP: systolic arterial pressure;
516 DAP: diastolic arterial pressure * $p < 0.05$ vs. CG. # $p < 0.05$ vs. CG supine.

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Table 3. Closed loop indices of the control (CG) and the fibromyalgia syndrome (FMS) groups in supine and standing positions.

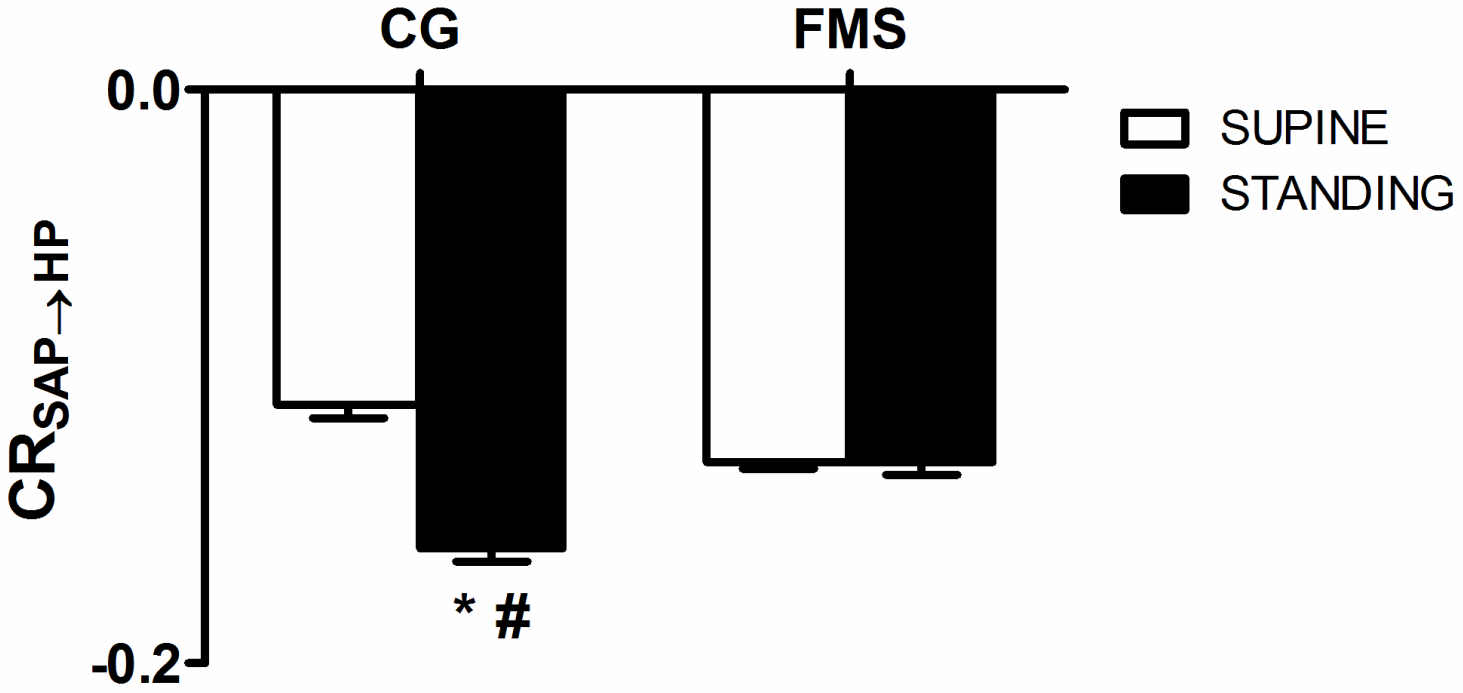
	Supine		Standing		P	G	I
	CG	FMS	CG	FMS			
α_{SEQ} (ms/mmHg)	13.5 ± 1.8	11.0 ±1.2	8.0 ±0.9	8.0 ± 0.8	<0.05	ns	ns
α_{LF} (ms/mmHg)	10.3 ± 1.7	8.0 ± 1.5	7.8 ± 0.8	5.6 ± 0.7	<0.05	ns	ns
α_{CL} (ms/mmHg)	5.0 ± 0.5*	2.1 ± 0.4	2.0 ± 0.6#	2.2 ± 0.5	<0.05	<0.05	<0.05
K_{CL} (mmHg/s)	-22.6 ± 2.5	-16.4 ± 2.2	-20.0 ± 2.5	-14.9 ± 3.4	ns	ns	ns

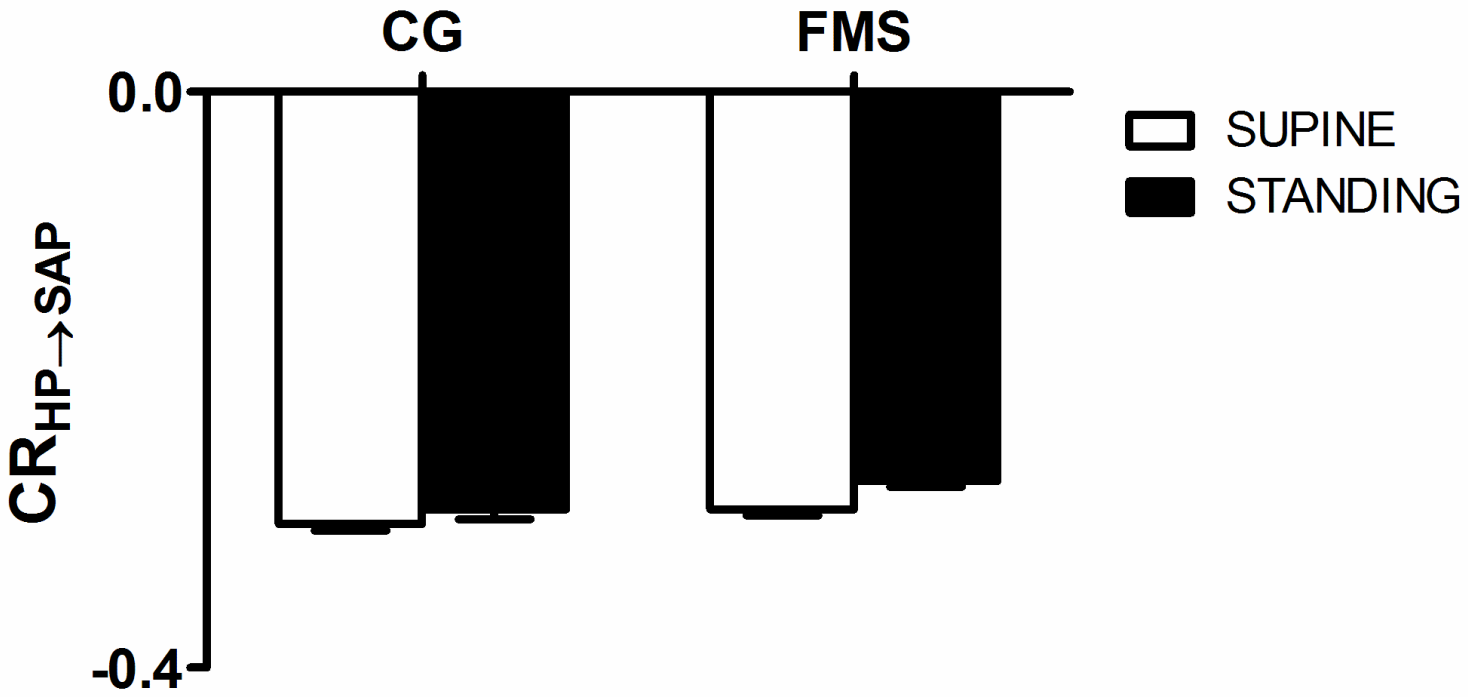
α_{SEQ}: baroreflex sensitivity estimate via sequence method; α_{LF}: baroreflex sensitivity estimate via spectral method in the low frequency band; α_{CL}: baroreflex sensitivity estimate via model-based closed-loop approach; K_{CL} gain of the mechanical feedforward arm of the HP-SAP closed-loop; P: posture main effect posture; G: group main effect; I: interaction. # $p < 0.05$ *vs* supine. * $p < 0.05$ *vs* FMS group.

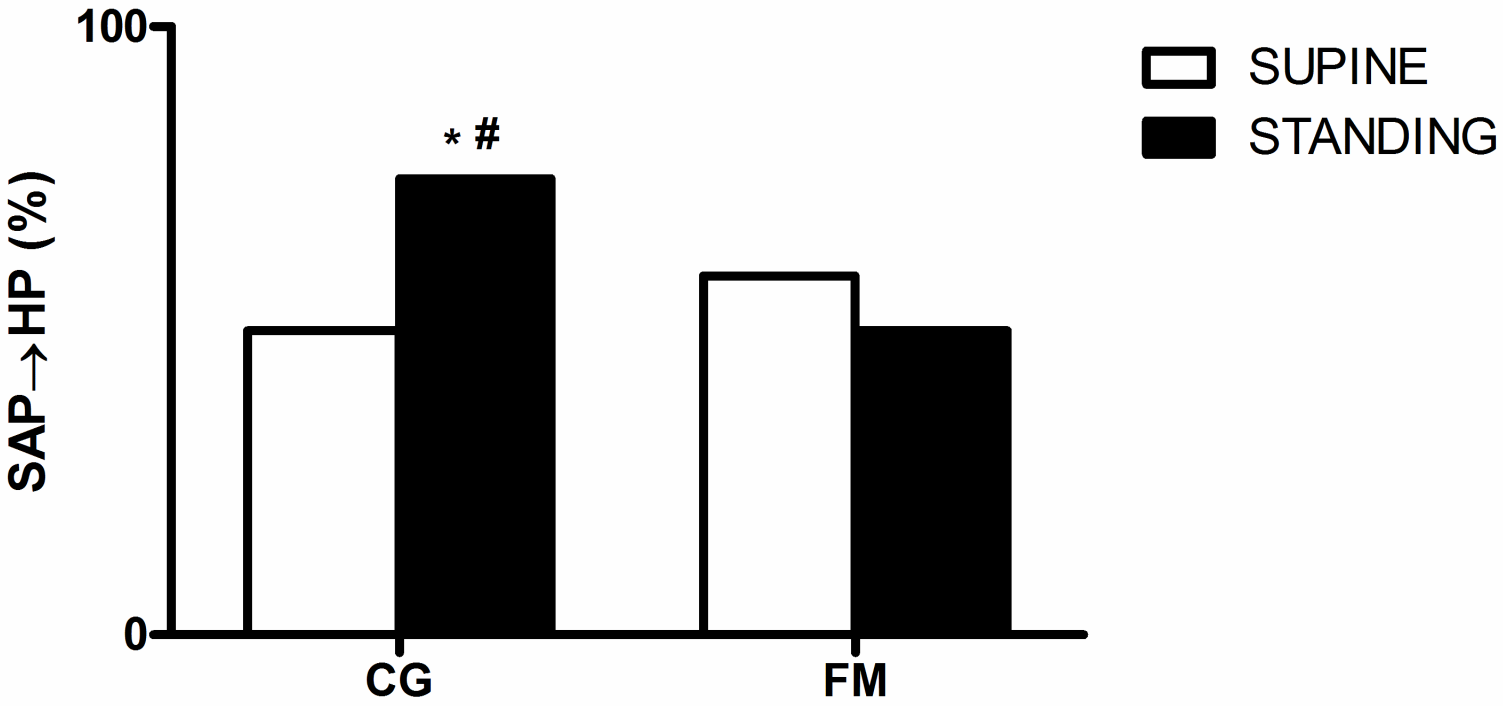
Table 4. Goodness of fit ρ^2 of the causal models explaining the series HP and SAP in Ω={HP, SAP, TSP}.

	Supine		Standing		P	G	I
	CG	FMS	CG	FMS			
ρ^2_{HP}	0.76 ± 0.12	0.75 ± 0.09	0.84 ± 0.08	0.78 ± 0.20	0.02	ns	ns
ρ^2_{SAP}	0.91 ± 0.07	0.92 ± 0.04	0.91 ± 0.06	0.87 ± 0.12	ns	ns	ns

CG: control group; FMS: fibromyalgia syndrome group.


CG
FMS
0.0
-0.2
$CR_{SAP \rightarrow HP}$
* #
SUPINE
STANDING


CG
FMS
0.0
-0.4
$CR_{HP \rightarrow SAP}$
SUPINE
STANDING


100
0
SAP→HP (%)
* #
CG
FM
SUPINE
STANDING